IJLST

ISSN: 0974-5335
IJLST (2008), 1(1):9-23

What is sleep and why is it needed?

Vibha Madan[1] and Sushil K Jha[2]

sushilkjha@mail.jnu.ac.in

[1] Department of Animal Biology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, USA
[2] School of Life Sciences, Jawaharlal Nehru University, New Delhi-110067, INDIA

Abstract:
The beginning of sleep research dates back to the late 19th or early 20th century. But there are several issues about sleep which still remain conundrum: 1) What is sleep and do all animals sleep? 2) Why do higher animals such as mammals and birds have different nature of sleep than fishes, amphibians and reptiles? 3) How is sleep generated and is there any sleep switch in the brain? 4) What is the purpose of sleep or why do we sleep? Since the discovery of polygraph by Hans Berger in 1929 and REM sleep by Eugene Aserinsky and Nathaniel Kleitman in 1953, sleep researchers have made significant discoveries and have solved several jigsaws but we still do not have answer to some very fundamental questions about sleep. Vast numbers of research articles advocate the importance of sleep in mammals, but its role in other lower animals is not known at all. Internet search on the pubmed with the keywords "why do we sleep" brings 468 articles while the google scholar search produces nearly 7,19,000 articles, but still all these articles are not sufficient enough to corroborate the purpose of sleep. Based on the available knowledge, we have attempted to review the possible cause of evolution and purpose of sleep in terrestrial mammals and the underlying neuronal mechanism of sleep generation.

Introduction

Sleep is a regular physiological state of natural lie down and is observed in majority of organisms [1]. It is an instinctive state of rest characterized by a reduction in voluntary body movement and decreased awareness of the surroundings [2]. Since consciousness is literally the awareness of the surroundings; being asleep is just an altered state of consciousness, as opposed to being unconscious. It is generated by complex but specific brain neuronal circuitry and heavily influenced by biological rhythms [3], hormonal changes [4] and also by environmental factors [5, 6]. During the last 50 years, particularly after the discovery of a unique sleep state identified as rapid eye movement (REM) sleep, several papers/reviews have been published regarding the neural mechanisms of sleep generation and its specific functions; but we are still far from triumph in solving the mystery of sleep.

Similar to any other biological process, sleep in vertebrates, has a progressive phylogenetic development [7]. Higher animals such as the birds and mammals exhibit two distinct types of behavioral and physiological sleep; non-REM (slow-wave) sleep and REM sleep, which proceed in cycles of different phases (five stages in human and mainly two-three stages in the rat, cat, dog and other mammals) [1, 7]. Sleep in other vertebrates such as fishes, amphibians and reptiles, is considered unitary in nature [8]. The raison d'être of the phylogenetic evolution of binary nature of sleep present in birds and terrestrial mammals as opposed to the unitary nature of amphibian and reptilian sleep is still unknown. Further, the brain cortical waves during sleep, obtained through electrophysiological recordings, differ greatly in lower vertebrates compared to the avian and mammalian species. For example: in frog, the observed forebrain electroencephalogram (EEG) exhibits high voltage during active states and minimum voltage during rest states, whereas mammalian and avian cortical EEG in contrast has high voltage during non-REM sleep and low voltage during wake and REM sleep [7, 9]. This suggests that brain waves associated with rest and/or sleep states are not universally similar across species adding complexity to the unsolved puzzle of the very nature and evolution of sleep.

Numerous theories have been proposed over the years regarding the functions of sleep; for example: sleep boosts up the immune functions, has a role in brain maturation and helps in energy conservation etc. [10, 11]. According to the ontogenetic hypothesis of REM sleep, the brain activity occurring during neonatal REM sleep seems to be particularly important to the

developing organism [12]. Studies investigating the effects of deprivation of REM sleep have shown that deprivation early in life can result in behavioral problems, permanent sleep disruption, decreased brain mass [13, 14], and an abnormal amount of neuronal cell death [15]. Another hypothesis is that sleep contributes to memory consolidation possibly by enhancing synaptic plasticity [11, 16, 17]. For example, REM sleep and pontine P-wave density (PGO wave) are reported to increase following successful learning in the rat [18]. Decrements in performance after sleep deprivation have been demonstrated in rats [19] and humans [16, 20]. Further, brain activity during sleep has been reported to 'replay' patterns elicited during initial training suggesting sleep-dependent neural processing of memory [21]. Though these studies suggest a crucial role of sleep but what has been lacking however, are more direct evidences showing the purpose of sleep for these functions. Given sleep's heterogeneous nature, no single theory predominates, as it is difficult to describe one single "function" of sleep.

The function, evolution and brain mechanism associated with the generation of sleep are not clearly understood. Since most of the research on sleep has been conducted in mammalian models, hence in this review, we would focus on these three aspects of sleep in modern and ancient mammals.

Evolution of sleep in mammals:

(a) Sleep in terrestrial and aquatic mammals:

Using standard electrophysiological criteria for sleep recording, sleep-wakefulness has been investigated in several terrestrial and aquatic animals; for example, in platypus [22], opossum [23], ferret [7], cat [24], rat [2, 25], mice [26], dog [27], monkey [28], dolphin [29], whale [30], seal [31], sea lion [32], etc. In standard practice, for polysomnographic characterization of sleep state into non-REM and REM sleep, electrophysiological signals from the electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG) are used. The low voltage and high frequency (desynchronized) EEG waves associated with increased motor activity are identified as wake (W). Epochs with high voltage and low frequency (synchronized) EEG waves (0.5 – 4 Hz) and decreased motor activity are characterized as non-REM sleep. Epochs with low voltage and high frequency EEG waves with a prominent theta peak (4 – 9 Hz) and nuchal muscle atonia are identified as REM sleep [Fig 1] [7].

Interestingly, the mammals completely adapted to land life, exhibit two distinct states of sleep i.e. non-REM and REM sleep [1], whereas aquatic mammals show either little or no sign of REM sleep [29, 30], thus exhibiting almost a unitary nature of sleep. Further, the REM sleep percent amount in old primitive terrestrial mammals, for example; the platypus [22] and the ferret [7] is quite high compared to the modern mammals [Fig 2] [7]. It is noteworthy that when on land, sleep in the fur seal generally resembles to sleep of most terrestrial mammals i.e. the bilateral EEG exhibits synchronization during non-REM sleep and desynchronization during REM sleep and sleep cycles alternate between non-REM and REM sleep [33, 34]. But when the fur seal is in water, the occurrence of REM sleep reduces exceptionally to the extent that there may not be even a single episode of REM sleep. Infact it also defies the principle of homeostatic regulation of sleep since no rebound of lost REM sleep is seen when the fur seal returns to land after staying several weeks in the water [34].

Adaptive forces also influence the sleep pattern in animals. Avian sleep has been influenced by arboreal adaptation. Although both non-REM and REM sleep has been reported in birds, the REM sleep episodes in them seem to be shorter in duration compared to the mammals [35]. On the other hand, the situation is quite different in the cetaceans (aquatic mammals) such as dolphins and whales [29, 30]. These animals show only unihemispheric sleep. They never show bilateral high-voltage EEG and also exhibit negligible amount or complete absence of REM sleep. This form of lateralized sleep behavior, known as unihemispheric slow wave sleep (USWS), is seen in all members of the order Cetacea examined till date [34]. Additional knowledge is needed to understand the cetaceans' somnogenic system as the possible selection pressures or aquatic adaptation might have helped in evolving such a unique nature of sleep. Fishes, amphibians and reptilians share the physiological correlates of brain waves during sleep or rest phase but similar to the aquatic mammalian life, they do not show

any sign of REM sleep [34]. In black (*Ctenosaura pectinata*) and green (*Iguana iguana*) iguanid lizards, EEGs are dominated by small amplitude monophasic sharp and saw-tooth waves during behavioral waking, while these become polymorphic and irregular in form during behavioral sleep [36]. In these animals, EEG frequencies slightly decline and amplitudes substantially diminish with sleep [36, 37].

The somnogenic pattern in the aquatic animals such as fishes and amphibians, or aquatic mammals such as cetaceans shows a marked absence or loss of REM sleep. It is known that the fishes and amphibians lead an aquatic life; while the limited studies about the sleep pattern in the reptiles shows that these animals have either adapted to aquatic life (such as turtles) or live near to the water body (such as black (*Ctenosaura pectinata*) and green *(Iguana iguana)* iguanid lizards). Further, the cetaceans which are aquatic mammals have no REM sleep and fur seal which is adapted to both terrestrial and aquatic life exhibit negligible amount of REM sleep when in water. Based on these findings we reason that the evolution of REM sleep is confined to the life on land only and it is the adaptation to the aquatic environment that inhibits the occurrence of REM sleep. It is possible that REM sleep serves some meaningful purpose only in the terrestrial mammals and birds and hence its evolution is confined to the land species only.

(b) Sleep in terrestrial herbivores and carnivores:

Feeding behavior also alters the daily sleep amounts in mammals. For example: carnivores, such as the bat and opossum, sleep for 18–20 hours a day while the big herbivores such as the elephant and giraffe, sleep for as little as 3–4 hours a day [1]. The customary diet in mammals is significantly correlated with their sleep time. Recently Prof Siegel from UCLA, USA, has reviewed that daily sleep amounts are highest in carnivores, lower in omnivores and lowest in herbivores [33]. Sleep time was highly significantly correlated with body mass in all mammals studied so far. When evaluated separately, the sleep time in herbivores was inversely correlated with their body mass while it was not significant in carnivores or omnivores [33].

Further, herbivores face consistent threat to be preyed and lower daily sleep amount, REM sleep in particular, in these animals is also viewed in the light of them staying in a safe and/or an unsafe environment. The vulnerability of the large herbivores in the wild suggests that it would be highly maladaptive for them to have a greatly reduced sensory responsiveness that defines sleep. Hunger, a normal condition in the wild, has been found to greatly reduce sleep in the rat [33], and it might be expected to do so in other species under conditions where waking would increase the probability of feeding. Conversely, when no food is likely to be found, increased sleep is the best survival strategy. From the primitive to the modern mammals and from the herbivores to the carnivores, daily sleep amount, primarily REM sleep amount, is highest among the more primitive carnivores like the platypus and lowest among the modern herbivores like the monkey [Fig 2] [7].

Generation of sleep in mammals:

(a) Neural mechanism of non-REM sleep generation:

Following the acceptance in the 1940s and 1950s of the existence of an activating system, many physiologists believed that sleep was the result of fatigue and decrease in activity of this system, thus representing a passive deactivation [38]. However, in experimental studies employing transections of the brainstem, it was found that sleep could be diminished indicating that active sleep-inducing structures must be present in the brain. Moruzzi and his colleagues were thus to show that transection of the brainstem behind the oral pontine tegmentum resulted in a total insomnia [39]. These results indicated that sleep-generating structures were located in the lower brainstem. Low frequency stimulation of medullary reticular formation within the medulla, particularly the dorsal reticular formation and the solitary tract nucleus, was shown to produce cortical synchronization indicative of non-REM (slow-wave) sleep in an awake animal preparation [40]. Conversely, lesions of the dorsal reticular formation and the nucleus of the solitary tract produced desynchronization of the EEG in sleeping animal preparation [41]. All these results suggested that neurons, in the dorsal medullary reticular formation and the nucleus of the solitary tract could generate sleep. The mechanism was hypothesized to involve inhibition of the rostrally

located neurons of the ascending activating system, although a direct synchronogenic influence upon forebrain system was also considered a possibility.
Original studies of Bremer, in 1935, utilizing the cerveau isole preparation had shown that synchronogenic structures must also be located in the forebrain [42]. Cortical synchrony was continuous in such preparations, in which the brainstem influence was removed. It was discovered that synchronous cortical activity could be driven or recruited by low frequency electrical stimulation of midline thalamus [43]. Hess and his colleagues subsequently showed that this stimulation also led to behavioral sleep and synchronized EEG in the animal with chronically indwelling electrodes, thus leading Hess to suggest that the thalamus is the head ganglion of sleep [44]. However, lesion studies showed that although the thalamus is necessary for the production of cortical spindles, it is not necessary for the generation of cortical slow waves and behavioral sleep, which persist following its complete ablation [45].

In humans, von Economo in 1928 had noted that in certain cases of "encephalitica lethargica" in which insomnia was the prominent symptom, lesions were centered in the anterior hypothalamus [46]. He thus postulated that a sleep facilitatory center was located in the anterior hypothalamus [46]. This sleep center was conceived to be in opposition to and normally in balance with the sleep inhibitory or waking center of the posterior hypothalamus. Nauta later experimentally confirmed the existence of a sleep facilitatory region in the anterior hypothalamus and preoptic area by knife cuts [47]. Hess demonstrated that electrical stimulation of this area could elicit behavioral suppression [48]. Neurons in this anterior region were postulated to exert an inhibitory influence upon the neurons of the ascending reticular activating system.

In the 1960s, Sterman and Clemente showed that electrical stimulation of the preoptic area and basal forebrain (including the nucleus of the diagonal band) led to drowsiness and behavioral sleep and synchronized EEG [49, 50]. Conversely, they found that lesion of basal forebrain, including the preoptic area, substantia innominata and nucleus of horizontal limb of the diagonal band, led to elimination or a decrease in sleep and a disruption of the sleep cycle [51, 52]. Villablanca and his colleagues found that animals without neocortex and striatum, thus called "diencephalic" cats and with sleep-inducing structures of both the lower brainstem and the anterior diencephalon largely intact did not show a normal sleep cycle, but instead a large decrease in sleeping time [53]. Electrical stimulation of both the caudate nucleus and the orbito-frontal cortex had been shown to produce cortical synchronization and behavioral sleep [54, 55]. Bilateral lesions of frontal cortex resulted in a permanent moderate reduction in sleep, whereas lesions of the caudate nuclei led to temporary decrease in sleep [54, 56].

From early neuroanatomical studies, neurons in the hypothalamus and preoptic area have been known to provide an innervation to limbic forebrain structures including notably the septum, amygdala and frontal cortex and also send descending projections to the limbic midbrain region, in what Nauta termed the "limbic forebrain-midbrain circuit" [57]. Such descending projections would allow for a certain degree of modulation of midbrain reticular formation, although the main projection is actually focused more medially onto the paramedian tegmentum, central gray and raphe nuclei [57-59]. Neurons in the hypothalamus as well as the bed nucleus of the stria terminalis and the amygdala also project directly to the solitary tract nucleus and the adjacent tegmentum in the medulla, sending fibers through as well as to the parabrachial region in the pons [60]. These forebrain and lower brainstem structures thus appear to form by their inter-connections a complex regulatory system which seems to be involved in sleep generation. Recently direct cholinergic projections from neurons in the basal forebrain to the cerebral cortex, originating from neurons in the substantia innominata, nuclei of the diagonal band, septum and magnocellular nuclei have been proposed to be involved in inducing cerebral activity [61].

(b) Neural mechanism of REM-sleep generation:

It was known since the work of the English physiologist Charles Sherrington that animals could survive removal of the entire forebrain. Using similar forebrain transections, Jouvet analyzed the sleep and waking states in "decerebrate" (without cerebrum) animals. He found that these decerebrate animals had periods

of muscle tone suppression with rapid eye movements resembling those seen during REM sleep [62]. In addition, the REM sleep like state in such animals recurred periodically and had some what similar duration as that in the intact animals. In related studies, brain transection between the pons and the midbrain resulted in the appearance of REM sleep signs only caudal to the cut [63, 64]. This demonstrated that the forebrain and midbrain might not be essential for the appearance of REM sleep. In an attempt to further narrow down the brainstem region responsible for REM sleep regulation, in different studies, transections were made along various planes in the brain stem. REM sleep associated signs could be observed only in the brain region that remained connected to the pons and it was concluded that the pontine region in the brainstem was both necessary and sufficient to generate the basic phenomenon of REM sleep [65]. Several other studies showed that damage to the pons altered REM sleep and the key region essential for REM sleep generation is in the lateral region of the reticular formation, in the nucleus 'pontis reticularis oralis' (PRO) and locus coeruleus (LC). Lesions of the PRO permanently eliminated all signs resembling REM sleep [66, 67]; whereas, lesions of LC significantly induced REM sleep [68]. Further, destruction of neurons around LC, led to an irreversible disappearance of atonia during REM sleep [69-72]. Reversible inactivation of LC by local cooling increased non-REM sleep as well as REM sleep [73]. These findings suggest that LC and PRO play an important role in REM sleep regulation.

Evidences also suggest the role of other pontine nuclei that could play a permissive and/or interactive role with the LC for REM sleep regulation. The potine region possesses anatomically distinct nuclear groups viz. nor-adrenergic (NA-ergic) neurons in the LC, acetylcholinergic (ACh-ergic) neurons in the latero-dorsal tegmentum (LDT) and pedunculo-pontine tegmentum (PPT), serotonergic (5-HT-ergic) neurons in the dorsal raphe nucleus (DRN) while GABA-ergic, glutamatergic and various peptidergic neurons scattered all over [2, 62, 74-78]. These heterogeneous populations of neurons in the pons project on each other and also receive projections from other brain areas containing dopaminergic and orexinergic neurotransmitters [79]. As mentioned earlier, lesion within pontine areas affects the appearance of REM sleep. Therefore, it is likely that among these heterogeneous pontine nuclei, some may be specifically REM sleep executive neurons.

Single unit recording studies identified two distinct populations of REM sleep specific neurons in the pontine region. One, which are continuously active in waking, slow down during non-REM sleep but are virtually silent during REM sleep; the "*REM-OFF*" neurons [74, 80, 81]. Others, which are almost inactive during waking and non-REM sleep, and fire exclusively during REM sleep; the "*REM-ON*" neurons [82]. The REM-OFF neurons are aminergic: NA-ergic [74], likely to be involved in muscle atonia; serotonergic, likely to be involved in the generation of the PGO waves [81, 83, 84] and histaminergic [85, 86]. The REM-ON cells are presumably cholinergic [72, 87, 88] although presence of some non-cholinergic REM-ON neurons has also been proposed [72, 87, 88]. These cells are mainly located in the paragigantocellular reticular formation and the LDT/PPT.

Three diffuse projection systems arising in the brainstem, the NA-ergic projections originating in the LC, the serotonergic projections from the DRN and the ACh-ergic projections from the LDT/PPT, may function as the controllers of sleep and wakefulness [89]. It has been proposed that the ascending projections from the LC are a component of the arousal system, while the function of the serotonergic projections is still not clearly known. The projections of the pontine cholinergic neurons to the cortex via thalamus play a role in EEG desynchrony during wakefulness and REM sleep. Thus, the findings indicate that the interactions between neurotransmitters play a significant role in modulating the neuronal behavior resulting in transition from one state to another, viz. wakefulness to non-REM sleep to REM sleep.

Functions of sleep in mammals:

We spend a third of our lives sleeping and most of us think we sleep to restore body and brain metabolic expenditure. This could be true, but we don't actually know why we sleep? If the rats are continuously deprived of sleep, they die after 12-14 days, although the actual cause of such death remains undetermined. Why do the rats die without sleep? Is it that sleep is indispensable for its survival? On the other hand, humans can

sustain there life till eleven days without sleeping and show no discernable ill effects apart from feeling sleepy. This obviously does not tell us much about why we sleep, only that we have a very powerful mechanism to make us sleep. But on the other hand, several papers suggest that sleep fulfills multiple functions and most among them are imperative for our survival.

Sleep researchers have attempted to identify the possible function(s) of sleep and this has generated a good deal of empirical research. Most of this research has involved either partial or total sleep deprivation. Using sleep-deprivation tools, a growing body of evidence indicates that even minor sleep loss, particularly if it accumulates over long period of time, has notable behavioral and cognitive consequences. Therefore, the changes in behavioral, metabolic and endocrine responses to lack of sleep have received a great deal of attention. It has been reported in human as well as animal studies that loss of sleep affects several behaviors leading to anxiety, irritability, aggressiveness [90], fighting [91], hypersexuality [92] and loss of concentration and memory consolidation [93, 94]. REM sleep deprived rats became extremely sensitive to tactile stimuli i.e. flinching, jumping and squealing when touched and became very aggressive [95]. Therefore, the findings of such deprivation research have great implications for the sleep function theories.

A series of related or somehow different set of hypothesis have been suggested such as: (1) sleep serves the purpose of cell maturation during ontogenic development; (2) sleep serves to dispose energy; (3) sleep serves the control of oculo-motor activity; (4) sleep maintains catecholamine levels in the brain; (5) sleep consolidates memory; and (6) sleep maintains life. Further, it modulates (7) metabolic processes at the molecular level; (8) synaptic neurotransmission at the subcellular level; (9) detoxification, restitution and proliferation at the cellular level; (10) thermoregulation; (11) neuroimmunoendocrine information processing at the physiological level; (12) antistress reactions and emotional fluctuations at the psychological level; (13) immune and host defense responses at the pathological level; (14) growth and time-keeping at the whole body level; (15) pregnancy and lactation at the reproductive level and (16) strategy for survival at the evolutionary level [96]. Hence, it can be seen that sleep has multi-dimensional functions and to review all these functions at one place would be an onerous task. Among numerous theories regarding the functions of sleep, one theory of sleep is that it enhances the neural mechanisms associated with memory storage [97] and synaptic plasticity (an underlying mechanism of sleep-dependent memory consolidation) [98]. Hence in this review, we have attempted to discuss and highlight the significant role of sleep in memory consolidation.

The important function of sleep is in the processing of learning information and the learned memory seems to be processed differentially by various stages of sleep such as REM and non-REM sleep. Sleep, after training, appears to influence the consolidation of certain non-declarative memories (e.g. procedural skill learning) in humans and experimental animals [16, 99, 100]. To understand the nature of the influence of sleep on consolidation of memories, it is important to first understand the various different types of memories and the neural systems involved in forming these memories.

Based on recollection of stored information in the brain with and without conscious effort, memories are most commonly divided into two main categories; declarative memory and non-declarative memory [Fig 3]. Declarative memories are those that a person can call to mind: for example, the president of India or the last movie you watched, and non-declarative memories are those that are normally used without conscious recollection: for example, how to drive a car, how to deal with aversive situations. Declarative memories are of two types: episodic and semantic memories. Non-declarative memories are also divided into several subcategories, such as procedural skills, conditioning (associative) memory, non-associative memory and priming.

These different forms or aspects of learning and memory involve different brain systems. The procedural memories for example involve the hippocampus–medial temporal lobe system while the associative memories involve the amygdala and cerebellum [101]. Under normal conditions, however, many of the brain–memory systems are engaged to some degree in learning situations, but each of the different brain area is learning something different about the situation. For example; the cerebellar system is learning to make specific behavioral responses that are most

adaptive in dealing with an aversive event. The amygdalar system is learning fear and associated autonomic responses to deal with the situation. The hippocampal system is learning what the situation is, i.e., experiential or episodic memories about the events and their relationships in context of the organism's ongoing experience [101].

Mechanism of memory consolidation:

After the initial encoding of sensorimotor experiences, a series of cellular, molecular and systems-level alterations develop over time that stabilizes and enhances the initial memory representation, converting it into a long-lasting and optimally integrated memory. A potential mechanism for memory storage is the induction of synaptic plasticity such as long term potentiation (LTP), which is induced by the activation of a cascade of cellular and molecular mechanisms, such as activation of NMDA receptors which open the Na^+/Ca^{2+} channels, activating several proteins and protein kinases (PKA), which in turn induce synaptic potentiation. These processes associated with consolidation of certain category of memories are thought to be sleep-dependent [98].

Role of sleep in memory consolidation:

Memory of procedural skill tasks shows the greatest evidence of sleep dependence. For example: in humans, a visual texture discrimination test, a motor sequence test and a motor adaptation test, demonstrated that all subjects show post-training improvement after a night's sleep but not during an equivalent period of being awake. The results also demonstrated that the amount of overnight improvement of procedural skills correlates with the amount of specific sleep stages and sleep deprivation can prevent the normal overnight improvement [16, 20].

Improvement in different learning tasks correlates significantly with different states of sleep. The multiplicities of sleep stages possibly, in part, provide optimal brain states for a range of distinct memory consolidation processes. For example: improvement in the visual texture discrimination task correlates with the levels of both sleep states: REM sleep and non-REM sleep [99], while improvement in the motor sequence task and the motor adaptation task correlates with non-REM sleep only [99, 100]. Thus, for these procedural skill tasks, sleep-dependent memory consolidation does not seem to depend consistently on one specific aspect of sleep; instead, each stage of sleep seems to contribute differently to these processes.

In rats, total/partial sleep deprivation and/or REM sleep deprivation affects different neural systems associated with procedural memory. For example, REM sleep deprivation exclusively affects the neural system associated with hippocampus dependent memory consolidation but does not affect the hippocampus independent memory consolidation [19, 102]. Spatial learning in the Morris water maze, configured to be hippocampus dependent, is a multi-trial task over multiple days in which animals learn to find a submerged, hidden platform in a pool of water by using spatial cues [103]. In rats, REM sleep deprivation after training for the hidden-platform version of the Morris water maze disrupts memory consolidation, as measured by an increase in the time taken to reach the hidden platform [19, 102]. Performance in the visible-platform version of the water maze, which is hippocampus-independent, is not affected by REM sleep deprivation [19, 102]. In a separate set of experiments, it was shown that REM sleep in rats is increased after training for the hidden-platform version, but not the visible-platform version, of the water maze [19]. These experiments examining spatial memory have provided important support for the idea that REM sleep plays a central role in the consolidation of hippocampus associated memory.

Role of sleep in associative conditioning:

Much has been learnt about the role of sleep in the consolidation of non-declarative procedural memory [99], but the role of sleep in the consolidation of associative memory is still not clear. Pavlovian fear conditioning is a paradigm that can be used to understand the role of sleep in associative memory. In pavlovian fear conditioning, the animal is trained to learn to fear a new environment (context) or a discrete conditioned stimulus (CS) because of the association between this CS with an aversive unconditioned stimulus (US), the foot shock [104, 105]. When exposed to the same context or cue after training, animals exhibit a variety of fear responses, such as altered REM sleep pattern, increased freezing behavior, ultrasonic vocalization etc. [106, 107]. The fear conditioning

paradigm has several advantages: (1) following a single trial, fear conditioning induces robust learning and memory, (2) it allows us to examine the consolidation of fearful memories dependent on the amygdalar and hippocampal functions, (3) it may enable a more thorough analysis of the time course of molecular changes associated with long-term memory consolidation and the influence of sleep on those changes.

The precise role of sleep in the consolidation of amygdalar and hippocampal associated fearful memory is not known. Some evidences suggest that it may 'facilitate' the consolidation of information of acquisition and expression of fearful response [104, 105, 108]. In cued fear conditioning, information of the CS reaches first to the lateral nucleus of the amygdala (LA) from the auditory thalamus and the auditory cortex. It is then relayed to other amygdaloid nuclei which in turn mediate the expression of conditioned emotional responses [104]. Simultaneous recording of neural activity in the medial geniculate nucleus (MGm) and LA neurons showed that neurons developed synaptic plasticity/LTP within few conditioned trials and these responses were re-expressed in REM sleep after conditioning. Further, there was a significant correlation between the response changes observed during conditioning and during REM sleep [109]. Conditioned heart rate accelerations to the CS tone were manifested in REM sleep after conditioning [110]. These studies suggest that some changes associated with conditioning occur during sleep, but we do not know if sleep just after training is vital for the consolidation of cued memory and if it is, then which sleep state (NREM sleep or REM sleep or both) plays a key function in this process. It has been observed that total sleep deprivation after training impairs memory consolidation of hippocampal dependent contextual memory but not the amygdalar dependent cued memory in C57BL/6 mice [111].

The consolidation of memory occurs over a period of hours to days and possibly depends on the short and/or long term reversible changes in the neuronal properties [98]. Following cued fear conditioning, the neuronal group in LA exhibits LTP [112, 113], which is RNA and protein synthesis dependent and requires the cAMP-dependent protein kinase (PKA) [114-116]. Several recent studies suggest that PKA activation and RNA and protein synthesis are also involved in fear memory consolidation. For example, blockade of PKA prevents LTP in the LA [117] and fear memory consolidation is impaired in transgenic mice that over express an inhibitory isoform of PKA [118]. Further, inhibitors of protein synthesis and PKA impair fear learning [119, 120]. The activity of cellular signaling pathways at different times after training is necessary for consolidation and could be sleep dependent. For instance, disruption of PKA signaling and protein synthesis at 0th hour and 4th hour but not 6th hour after training for fear conditioning disrupts long-term memory for this task [119]. On the other hand, sleep deprivation soon after training and up to 6 hrs impaired the performance of the given task suggesting that PKA signaling and protein synthesis associated with memory consolidation could be sleep dependent. Hence, sleep possibly facilitates PKA signaling and protein synthesis necessary for memory consolidation.

Conclusions:

Sleep timing varies greatly among mammals, from three hours in the elephant to twenty hours in the armadillo. Further, REM sleep amount is higher in most primitive mammals (the platypus and the ferret) and lower in most modern mammals. But surprisingly, REM sleep has not been reported in the reptiles, from which the first mammal has evolved in the world. This raises the doubt about the origin and evolution of REM sleep and also the purpose of REM sleep evolution in the mammals. The misapprehension about the sleep generation started from the late 19^{th} and early 20^{th} century, when it was considered that sleep is the intermediate state between wakefulness and death; wakefulness is regarded as the active state of all the physical and intellectual functions, and death as that of their total suspension. So sleep was seen as passive and inactive phase during which body/brain lacks of their activity. It was thought that the sleeping brain is forced into wakefulness by the bombarding of the brain by sensory input, which then produced an active state in the brain. With the discovery of hypnogenic and wake centers in the brain the concept about sleep generation has changed dramatically. The influence of external factors and biological clock on its regulation and/or modulation has brought substantial clues to our knowledge about its generation and purpose. Several studies show the importance of two distinct stages of sleep: non-REM and REM

sleep, in mammals and birds, and have suggested its important role in the maintenance of several physiological functions although direct evidences are still lacking. Future studies might pull off a clear picture about the nature of sleep and neural circuitry in sleeping brain that adds to our health and cognition.

Acknowledgements:
Funding to SKJ from CSIR and DBT, India, is acknowledged.

References:

[1] H. Zeplin, J. M. Siegel and I. Tobler, "Mammalian sleep". In: M. H. Kryger, T. Roth and W. C. Dement (eds). *"Principles and practice of sleep medicine"*. Philadelphia: WB Saunders Company; 2005, pp. 91-100.

[2] B. N. Mallick, V. Madan and S. K. Jha, "Rapid Eye Movement Sleep Regulation by Modulation of Noradrenergic System". In: J. Monti, S. R. Pandi-Perumal and C. M. Sinton (eds). *"Neurochemistry of Sleep and Wakefulness"*. New York: Cambridge University Press,; 2008, pp. 59-84.

[3] C. A. Czeisler and J. J. Gooley, "Sleep and Circadian Rhythms in Humans", Cold Spring Harbor Symposia on Quantitative Biology, 2007, 72(1), pp. 579-597.

[4] D. P. Cardinali, S. R. Pandi-Perumal and L. P. Niles, "Melatonin and its receptors: biological function in circadian sleep–wake regulation". In: J. Monti, S. R. Pandi-Perumal and C. M. Sinton (eds). *"Neurochemistry of Sleep and Wakefulness"*. New York: Cambridge University Press; 2008, pp. 283-314.

[5] S. K. Jha, F. X. Brennan, A. C. Pawlyk, R. J. Ross and A. R. Morrison, "REM sleep: a sensitive index of fear conditioning in rats", Eur J Neurosci, 2005, 21(4), pp. 1077-1080.

[6] A. C. Pawlyk, S. K. Jha, F. X. Brennan, A. R. Morrison and R. J. Ross, "A rodent model of sleep disturbances in posttraumatic stress disorder: the role of context after fear conditioning", Biol Psychiatry, 2005, 57(3), pp. 268-277.

[7] S. K. Jha, T. Coleman and M. G. Frank, "Sleep and sleep regulation in the ferret (Mustela putorius furo)", Behav Brain Res, 2006, 172(1), pp. 106-113.

[8] M. C. Nicolau, M. Akaarir, A. Gamundi, J. Gonzalez and R. V. Rial, "Why we sleep: the evolutionary pathway to the mammalian sleep", Prog Neurobiol, 2000, 62(4), pp. 379-406.

[9] T. Yokogawa, W. Marin, J. Faraco, G. Pezeron, L. Appelbaum, J. Zhang, F. Rosa, P. Mourrain and E. Mignot, "Characterization of sleep in zebrafish and insomnia in hypocretin receptor mutants", PLoS Biol, 2007, 5(10), pp. 2379-2397.

[10] A. Rechtschaffen, "Current perspectives on the function of sleep", Perspect Biol Med, 1998, 41(3), pp. 359-390.

[11] L. Graves, A. Pack and T. Abel, "Sleep and memory: a molecular perspective", Trends Neurosci, 2001, 24(4), pp. 237-243.

[12] G. A. Marks, J. P. Shaffery, A. Oksenberg, S. G. Speciale and H. P. Roffwarg, "A functional role for REM sleep in brain maturation", Behav Brain Res, 1995, 69(1-2), pp. 1-11.

[13] M. Mirmiran, J. Scholtens, N. E. van de Poll, H. B. Uylings, J. van der Gugten and G. J. Boer, "Effects of experimental suppression of active (REM) sleep during early development upon adult brain and behavior in the rat", Brain Res, 1983, 283(2-3), pp. 277-286.

[14] M. Mirmiran, H. B. Uylings and M. A. Corner, "Pharmacological suppression of REM sleep prior to weaning counteracts the effectiveness of subsequent environmental enrichment on cortical growth in rats", Brain Res, 1983, 283(1), pp. 102-105.

[15] M. J. Morrissey, S. P. Duntley, A. M. Anch and R. Nonneman, "Active sleep and its role in the prevention of apoptosis in the developing brain", Med Hypotheses, 2004, 62(6), pp. 876-879.

[16] R. Stickgold, J. A. Hobson, R. Fosse and M. Fosse, "Sleep, learning, and dreams: off-line memory reprocessing", Science, 2001, 294(5544), pp. 1052-1057.

[17] S. K. Jha, B. E. Jones, T. Coleman, N. Steinmetz, C. T. Law, G. Griffin, J. Hawk, N. Dabbish, V. A. Kalatsky and M. G. Frank, "Sleep-dependent plasticity requires cortical activity", J Neurosci, 2005, 25(40), pp. 9266-9274.

[18] S. Datta, "Avoidance task training potentiates phasic pontine-wave density in the rat: A mechanism for sleep-dependent plasticity", J Neurosci, 2000, 20(22), pp. 8607-8613.

[19] C. Smith and G. M. Rose, "Evidence for a paradoxical sleep window for place learning in

the Morris water maze", Physiol Behav, 1996, 59(1), pp. 93-97.

[20] R. Stickgold, D. Whidbee, B. Schirmer, V. Patel and J. A. Hobson, "Visual discrimination task improvement: A multi-step process occurring during sleep", J Cogn Neurosci, 2000, 12(2), pp. 246-254.

[21] W. E. Skaggs and B. L. McNaughton, "Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience", Science, 1996, 271(5257), pp. 1870-1873.

[22] J. M. Siegel, P. R. Manger, R. Nienhuis, H. M. Fahringer, T. Shalita and J. D. Pettigrew, "Sleep in the platypus", Neuroscience, 1999, 91(1), pp. 391-400.

[23] H. Van Twyver and T. Allison, "Sleep in the opossum Didelphis marsupialis", Electroencephalogr Clin Neurophysiol, 1970, 29(2), pp. 181-189.

[24] R. Ursin, "The two stages of slow wave sleep in the cat and their relation to REM sleep", Brain Res, 1968, 11(2), pp. 347-356.

[25] S. K. Jha, R. J. Ross and A. R. Morrison, "Sleep-related neurons in the central nucleus of the amygdala of rats and their modulation by the dorsal raphe nucleus", Physiol Behav, 2005, 86(4), pp. 415-426.

[26] M. G. Frank, R. Morrissette and H. C. Heller, "Effects of sleep deprivation in neonatal rats", Am J Physiol, 1998, 275(1 Pt 2), pp. R148-157.

[27] C. Brisbare-Roch, J. Dingemanse, R. Koberstein, P. Hoever, H. Aissaoui, S. Flores, C. Mueller, O. Nayler, J. van Gerven, S. L. de Haas, P. Hess, C. Qiu, S. Buchmann, M. Scherz, T. Weller, W. Fischli, M. Clozel and F. Jenck, "Promotion of sleep by targeting the orexin system in rats, dogs and humans", Nat Med, 2007, 13(2), pp. 150-155.

[28] D. M. Edgar, W. C. Dement and C. A. Fuller, "Effect of SCN lesions on sleep in squirrel monkeys: evidence for opponent processes in sleep-wake regulation", J Neurosci, 1993, 13(3), pp. 1065-1079.

[29] L. M. Mukhametov, "Unihemispheric slow-wave sleep in the Amazonian dolphin, Inia geoffrensis", Neurosci Lett, 1987, 79(1-2), pp. 128-132.

[30] O. I. Lyamin, L. M. Mukhametov, J. M. Siegel, E. A. Nazarenko, I. G. Polyakova and O. V. Shpak, "Unihemispheric slow wave sleep and the state of the eyes in a white whale", Behav Brain Res, 2002, 129(1-2), pp. 125-129.

[31] S. H. Ridgway, R. J. Harrison and P. L. Joyce, "Sleep and cardiac rhythm in the gray seal", Science, 1975, 187(4176), pp. 553-555.

[32] O. I. Lyamin, L. M. Mukhametov, I. S. Chetyrbok and A. V. Vassiliev, "Sleep and wakefulness in the southern sea lion", Behav Brain Res, 2002, 128(2), pp. 129-138.

[33] J. M. Siegel, "Clues to the functions of mammalian sleep", Nature, 2005, 437(7063), pp. 1264-1271.

[34] J. M. Siegel, "Do all animals sleep?" Trends in Neurosciences, 2008, 31(4), pp. 208-213.

[35] C. J. Amlaner and N. J. Ball, "Avian sleep". In: M. H. Kryger, T. Roth and W. C. Dement (eds). *"Principles and Practice of Sleep Medicine"*. Philadelphia: W.B. Saunders Company; 2001, pp. 23-36.

[36] W. F. Flanigan, Jr., "Sleep and wakefulness in iguanid lizards, Ctenosaura pectinata and Iguana iguana", Brain Behav Evol, 1973, 8(6), pp. 401-436.

[37] F. Ayala-Guerrero and S. Huitron-Resendiz, "Sleep patterns in the lizard Ctenosaura pectinata", Physiol Behav, 1991, 49(6), pp. 1305-1307.

[38] G. Moruzzi, "*The sleep-waking cycle Ergebn Physiol*". New York: Springer-Verlag; 1972.

[39] C. Batini, G. Moruzzi, M. Palestini, G. F. Rossi and A. Zanchetti, "Persistent patterns of wakefulness in the pretrigeminal midpontine preparation", Science, 1958, 128, pp. 30-32.

[40] J. Magnes, G. Moruzzi and O. Pompeiano, "Synchronization of the EEG produced by low frequency electrical stimulation of the region of the solitary tract", Arch. It. Biol., 1961, (99), pp. 33-67.

[41] M. Bonvallet and M. B. Allen, Jr., "Prolonged Spontaneous and Evoked Reticular Activation Following Discrete Bulbar Lesions", Electroencephalogr Clin Neurophysiol, 1963, 15, pp. 969-988.

[42] F. Bremer, "Cerveau 'isolé' et physiologie du sommeil", C.R. Soc. Biol., 1935, 118, pp. 1235-1241.

[43] R. S. Morrision and E. W. Dempsey, "Mechanism of thalamocortical augmentation and repetition", Am J Physiol, 1942, 138, pp. 297-308.

[44] K. Akert, W. P. Koella and R. Hess, "Sleep produced by electrical stimulation of the thalamus", Am J Physiol, 1952, 168, pp. 260-267.

[45] J. Villablanca and M. E. Salinas-Zeballos, "Sleep-wakefulness, EEG and behavioral studies of chronic cats without the thalamus: the 'athalamic' cat", Arch Ital Biol, 1972, 110(3), pp. 383-411.

[46] C. von Economo, "Théorie du sommeil", J. Neurol. Psychiat, 1928, 7, pp. 437-464.

[47] W. J. H. Nauta, "Hypothalamic regulation of sleep in rats", J. Neurophysiol, 1946, 9, pp. 285-316.

[48] W. R. Hess, "The diencephalic sleep centre". In: J. F. Delafresnaye (ed). *"Brain Mechanisms and Consciousness"*. Oxford: Blackwell; 1954, pp. 117-136.

[49] M. B. Sterman and C. D. Clemente, "Forebrain inhibitory mechanisms: sleep patterns induced by basal forebrain stimulation in the behaving cat", Exp Neurol, 1962, 6, pp. 103-117.

[50] M. B. Sterman and C. D. Clemente, "Forebrain inhibitory mechanisms: cortical synchronization induced by basal forebrain stimulation", Exp Neurol, 1962, 6, pp. 91-102.

[51] D. J. McGinty and M. B. Sterman, "Sleep suppression after basal forebrain lesions in the cat", Science, 1968, 160(833), pp. 1253-1255.

[52] E. A. Lucas and M. B. Sterman, "Effect of a forebrain lesion on the polycyclic sleep-wake cycle and sleep-wake patterns in the cat", Exp Neurol, 1975, 46(2), pp. 368-388.

[53] J. Villablanca and R. Marcus, "Sleep-wakefulness, EEG and behavioral studies of chronic cats without neocortex and striatum: the 'diencephalic' cat", Arch Ital Biol, 1972, 110(3), pp. 348-382.

[54] J. H. Penaloza-Rojas, M. Eltherman and N. Olmos, "Sleep Induced by Cortical Stimulation", Exp Neurol, 1964, 10, pp. 140-147.

[55] S. L. Liles and G. D. Davis, "Electrocortical effects of caudate stimulations which alter cortically induced movement", J Neurophysiol, 1969, 32(4), pp. 574-582.

[56] S. L. Liles and G. D. Davis, "Interrelation of caudate nucleus and thalamus in alteration of cortically induced movement", J Neurophysiol, 1969, 32(4), pp. 564-573.

[57] W. J. H. Nauta and W. Haymaker, "Hypothalamic nuclei and fiber connections". In: W. Haymaker, E. Anderson and W. J. H. Nauta (eds). *"The Hypothalamus"*. Springfield: C. C. Thomas; 1969.

[58] L. W. Swanson, "An autoradiographic study of the efferent connections of the preoptic region in the rat", J Comp Neurol, 1976, 167(2), pp. 227-256.

[59] L. W. Swanson and W. M. Cowan, "The connections of the septal region in the rat", J Comp Neurol, 1979, 186(4), pp. 621-655.

[60] J. A. Ricardo and E. T. Koh, "Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala, and other forebrain structures in the rat", Brain Res, 1978, 153(1), pp. 1-26.

[61] R. Szymusiak, "Magnocellular nuclei of the basal forebrain: substrates of sleep and arousal regulation", Sleep, 1995, 18(6), pp. 478-500.

[62] M. Jouvet, "Paradoxical Sleep--a Study of Its Nature and Mechanisms", Prog Brain Res, 1965, 18, pp. 20-62.

[63] J. Villablanca, "The electrocorticogram in the chronic cerveau isole cat", Electroencephalogr Clin Neurophysiol, 1965, 19(6), pp. 576-586.

[64] J. Villablanca, "Behavioral and polygraphic study of "sleep" and "wakefulness" in chronic decerebrate cats", Electroencephalogr Clin Neurophysiol, 1966, 21(6), pp. 562-577.

[65] J. M. Siegel, K. S. Tomaszewski and R. Nienhuis, "Behavioral states in the chronic medullary and midpontine cat", Electroencephalogr Clin Neurophysiol, 1986, 63(3), pp. 274-288.

[66] G. Carli and A. Zanchetti, "A study of pontine lesions suppressing deep sleep in the cat", Arch Ital Biol, 1965, 103(4), pp. 751-788.

[67] J. P. Sastre, K. Sakai and M. Jouvet, "Are the gigantocellular tegmental field neurons responsible for paradoxical sleep?" Brain Res, 1981, 229(1), pp. 147-161.

[68] A. Caballero and I. De Andres, "Unilateral lesions in locus coeruleus area enhance paradoxical sleep", Electroencephalogr Clin Neurophysiol, 1986, 64(4), pp. 339-346.

[69] M. Jouvet and F. Delorme, "Locus coeruleus et sommeil paradoxal", Comp. Ren. Soc. de Biol., 1965, 159, pp. 895-899.

[70] K. Henley and A. R. Morrison, "A re-evaluation of the effects of lesions of the pontine tegmentum and locus coeruleus on phenomena of paradoxical sleep in the cat", Acta Neurobiol Exp (Wars), 1974, 34(2), pp. 215-232.

[71] C. M. Braun and R. T. Pivik, "Effects of locus coeruleus lesions upon sleeping and waking in the rabbit", Brain Res, 1981, 230(1-2), pp. 133-151.

[72] K. Sakai, "Some anatomical and physiological properties of ponto-mesencephalic tegmental neurons with special reference to the PGO waves and postural atonia during paradoxical sleep in cat". In: J. A. Hobson and M. A. B. Brazier (eds). *"The reticular formation revisited"*. New York: Raven Press; 1980, pp. 427-447.

[73] R. Cespuglio, M. E. Gomez, H. Faradji and M. Jouvet, "Alterations in the sleep-waking cycle induced by cooling of the locus coeruleus area", Electroencephalogr Clin Neurophysiol, 1982, 54(5), pp. 570-578.

[74] G. Aston-Jones and F. E. Bloom, "Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle", J Neurosci, 1981, 1(8), pp. 876-886.

[75] B. L. Jacobs, C. A. Fornal and L. O. Wilkinson, "Neurophysiological and neurochemical studies of brain serotonergic neurons in behaving animals", Ann N Y Acad Sci, 1990, 600, pp. 260-268; discussion 268-271.

[76] B. L. Jacobs, L. O. Wilkinson and C. A. Fornal, "The role of brain serotonin. A neurophysiologic perspective", Neuropsychopharmacology, 1990, 3(5-6), pp. 473-479.

[77] B. N. Mallick, S. Kaur, S. K. Jha and J. M. Siegel, "Possible role of GABA in the regulation of REM sleep with special reference to REM-OFF neurons". In: B. N. Mallick and S. Inoue (eds). *"Rapid eye movement sleep"*. New Yark: Marcel Dekker; 1999, pp. 153-166.

[78] B. N. Mallick, S. Thankachan and F. Islam, "Influence of hypnogenic brain areas on wakefulness- and rapid-eye-movement sleep-related neurons in the brainstem of freely moving cats", J Neurosci Res, 2004, 75(1), pp. 133-142.

[79] R. Winsky-Sommerer, B. Boutrel and L. De Lecea, "The role of the hypocretinergic system in the integration of networks that dictate the states of arousal", Drug News Perspect, 2003, 16(8), pp. 504-512.

[80] B. L. Jacobs, "Single unit activity of locus coeruleus neurons in behaving animals", Prog Neurobiol, 1986, 27(2), pp. 183-194.

[81] J. Heym, G. F. Steinfels and B. L. Jacobs, "Activity of serotonin-containing neurons in the nucleus raphe pallidus of freely moving cats", Brain Res, 1982, 251(2), pp. 259-276.

[82] J. A. Hobson, R. W. McCarley and P. W. Wyzinski, "Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups", Science, 1975, 189(4196), pp. 55-58.

[83] D. J. McGinty and R. M. Harper, "Dorsal raphe neurons: depression of firing during sleep in cats", Brain Res, 1976, 101(3), pp. 569-575.

[84] C. Fornal, S. Auerbach and B. L. Jacobs, "Activity of serotonin-containing neurons in nucleus raphe magnus in freely moving cats", Exp Neurol, 1985, 88(3), pp. 590-608.

[85] B. E. Jones, "From waking to sleeping: neuronal and chemical substrates", Trends Pharmacol Sci, 2005, 26(11), pp. 578-586.

[86] C. B. Saper, T. E. Scammell and J. Lu, "Hypothalamic regulation of sleep and circadian rhythms", Nature, 2005, 437(7063), pp. 1257-1263.

[87] M. el Mansari, K. Sakai and M. Jouvet, "Unitary characteristics of presumptive cholinergic tegmental neurons during the sleep-waking cycle in freely moving cats", Exp Brain Res, 1989, 76(3), pp. 519-529.

[88] H. A. Baghdoyan and R. Lydic, "Neurotransmitters and neuromodulators regulating sleep". In: C. W. Bazil (ed). *"Sleep and Epilepsy: The clinical Spectrum"*. New Yark: Elsevier Science; 2002, pp. 17-44.

[89] Y. Kayama and Y. Koyama, "Brainstem neural mechanisms of sleep and wakefulness", Eur Urol, 1998, 33 Suppl 3, pp. 12-15.

[90] W. C. Dement and C. Fischer, "Experimental intereference with the sleep cycle", J Can Psychiat Assoc, 1963, (8), pp. 400.

[91] B. Morden, R. Conner, G. Mitchell, W. C. Dement and S. Levine, "Effects of rapid eye movement sleep deprivation on shock induced fighting", Physiol Behav, 1968, (3), pp. 425-462.

[92] W. Dement, P. Henry, H. Cohen and J. Ferguson, "Studies on the effect of REM deprivation in humans and in animals", Res Publ Assoc Res Nerv Ment Dis, 1967, 45, pp. 456-468.

[93] W. Fishbein and B. M. Gutwein, "Paradoxical sleep and memory storage processes", Behav Biol, 1977, 19(4), pp. 425-464.

[94] C. T. Smith, J. M. Conway and G. M. Rose, "Brief paradoxical sleep deprivation impairs reference, but not working, memory in the radial arm maze task", Neurobiol Learn Mem, 1998, 69(2), pp. 211-217.

[95] C. A. Kushida, B. M. Bergmann and A. Rechtschaffen, "Sleep deprivation in the rat: IV. Paradoxical sleep deprivation", Sleep, 1989, 12(1), pp. 22-30.

[96] M. G. Frank, "The mystery of sleep function: current perspectives and future directions", Rev Neurosci, 2006, 17(4), pp. 375-392.

[97] M. G. Frank and J. H. Benington, "The role of sleep in memory consolidation and brain plasticity: dream or reality?" Neuroscientist, 2006, 12(6), pp. 477-488.

[98] J. H. Benington and M. G. Frank, "Cellular and molecular connections between sleep and synaptic plasticity", Prog Neurobiol, 2003, 69(2), pp. 71-101.

[99] R. Stickgold, "Sleep-dependent memory consolidation", Nature, 2005, 437(7063), pp. 1272-1278.

[100] R. Huber, M. F. Ghilardi, M. Massimini and G. Tononi, "Local sleep and learning", Nature, 2004, 430(6995), pp. 78-81.

[101] R. F. Thompson and J. J. Kim, "Memory systems in the brain and localization of a memory", Proc Natl Acad Sci U S A, 1996, 93(24), pp. 13438-13444.

[102] C. Smith, "Sleep states, memory processes and synaptic plasticity", Behav Brain Res, 1996, 78(1), pp. 49-56.

[103] R. G. Morris, P. Garrud, J. N. Rawlins and J. O'Keefe, "Place navigation impaired in rats with hippocampal lesions", Nature, 1982, 297(5868), pp. 681-683.

[104] J. E. LeDoux, "Emotion circuits in the brain", Annu Rev Neurosci, 2000, 23, pp. 155-184.

[105] S. Maren, "Neurobiology of Pavlovian fear conditioning", Annu Rev Neurosci, 2001, 24, pp. 897-931.

[106] M. S. Fanselow, "Conditioned and unconditional components of post-shock freezing." Pavlon J Biol Sci, 1980, 15(4), pp. 177-182.

[107] R. J. Blanchard and D. C. Blanchard, "Crouching as an index of fear", J Comp Physiol Psychol, 1969, 67(3), pp. 370-375.

[108] M. Davis and P. J. Whalen, "The amygdala: vigilance and emotion", Mol Psychiatry, 2001, 6(1), pp. 13-34.

[109] E. Hennevin, C. Maho and B. Hars, "Neuronal plasticity induced by fear conditioning is expressed during paradoxical sleep: evidence from simultaneous recordings in the lateral amygdala and the medial geniculate in rats", Behav Neurosci, 1998, 112(4), pp. 839-862.

[110] C. Maho and E. Hennevin, "Expression in paradoxical sleep of a conditioned heart rate response", Neuroreport, 1999, 10(16), pp. 3381-3385.

[111] L. A. Graves, E. A. Heller, A. I. Pack and T. Abel, "Sleep deprivation selectively impairs memory consolidation for contextual fear conditioning", Learn Mem, 2003, 10(3), pp. 168-176.

[112] M. G. McKernan and P. Shinnick-Gallagher, "Fear conditioning induces a lasting potentiation of synaptic currents in vitro", Nature, 1997, 390(6660), pp. 607-611.

[113] M. T. Rogan, U. V. Staubli and J. E. LeDoux, "Fear conditioning induces associative long-term potentiation in the amygdala", Nature, 1997, 390(6660), pp. 604-607.

[114] U. Frey, Y. Y. Huang and E. R. Kandel, "Effects of cAMP simulate a late stage of LTP in hippocampal CA1 neurons", Science, 1993, 260(5114), pp. 1661-1664.

[115] Y. Y. Huang, X. C. Li and E. R. Kandel, "cAMP contributes to mossy fiber LTP by initiating both a covalently mediated early phase and macromolecular synthesis-dependent late phase", Cell, 1994, 79(1), pp. 69-79.

[116] P. V. Nguyen and E. R. Kandel, "A macromolecular synthesis-dependent late phase of long-term potentiation requiring cAMP in the medial perforant pathway of rat hippocampal slices", J Neurosci, 1996, 16(10), pp. 3189-3198.

[117] Y. Y. Huang and E. R. Kandel, "Postsynaptic induction and PKA-dependent expression of LTP in the lateral amygdala", Neuron, 1998, 21(1), pp. 169-178.

[118] T. Abel, P. V. Nguyen, M. Barad, T. A. Deuel, E. R. Kandel and R. Bourtchouladze, "Genetic demonstration of a role for PKA in the late phase of LTP and in hippocampus-based

long-term memory", Cell, 1997, 88(5), pp. 615-626.

[119] R. Bourtchouladze, T. Abel, N. Berman, R. Gordon, K. Lapidus and E. R. Kandel, "Different training procedures recruit either one or two critical periods for contextual memory consolidation, each of which requires protein synthesis and PKA", Learn Mem, 1998, 5(4-5), pp. 365-374.

[120] G. E. Schafe, N. V. Nadel, G. M. Sullivan, A. Harris and J. E. LeDoux, "Memory consolidation for contextual and auditory fear conditioning is dependent on protein synthesis, PKA, and MAP kinase", Learn Mem, 1999, 6(2), pp. 97-110.

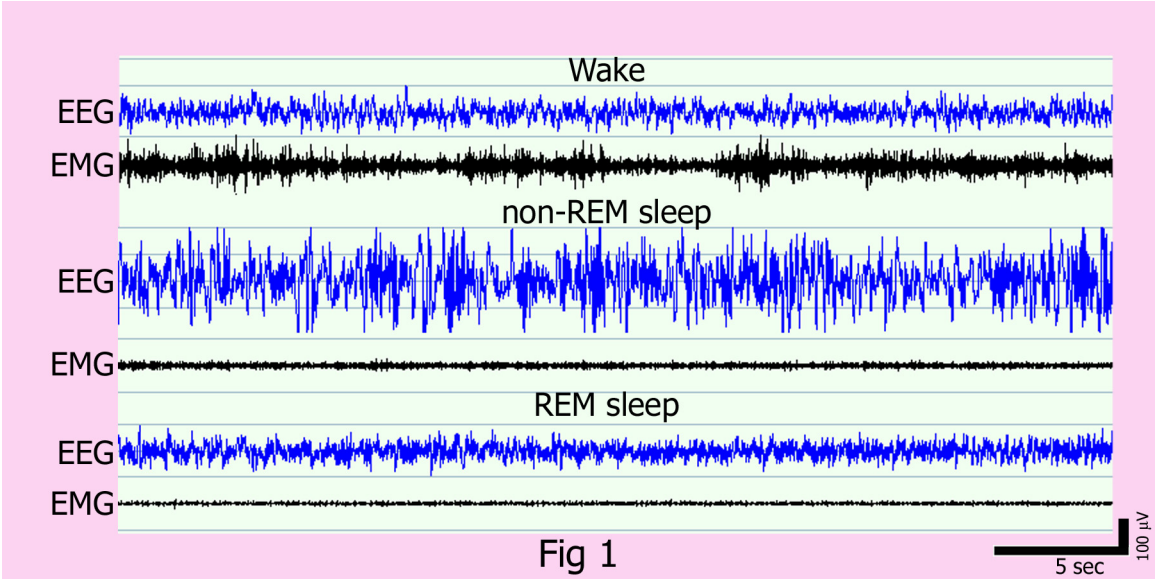

Figure 1. Representative polygraphic traces of the rat EEG and EMG showing different vigilance states. The upper trace with low voltage EEG and high EMG activity is the wake state, middle trace with high voltage and low EMG activity represents non-REM sleep state, while the lower trace with low voltage EEG but almost no EMG activity is the REM sleep state.

ISSN: 0974-5335
IJLST (2008), 1(1):9-23

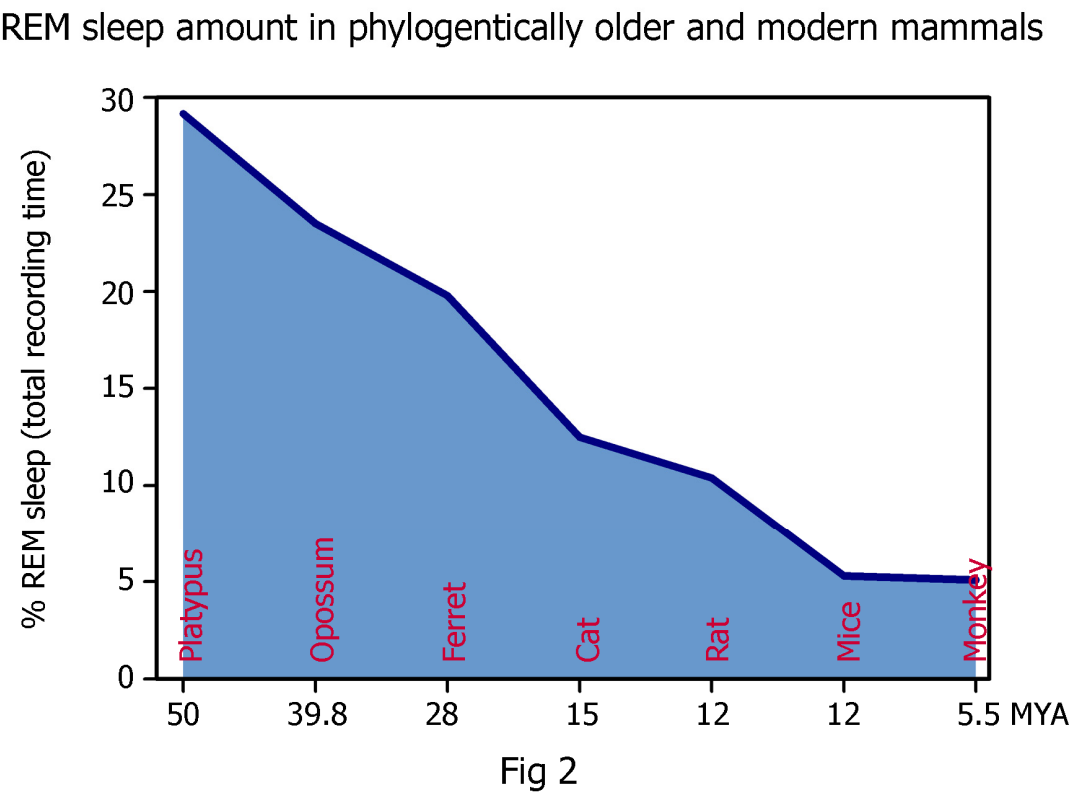

Figure 2. The REM sleep state occurs in high proportion in primitive terrestrial mammals compared to the modern terrestrial mammals. Please note that the platypus is an egg laying mammal and has evolved 50 million years ago (MYA), where as the monkey is a modern mammal and has evolved only 5.5 MYA. Phylogenetically, most of the ancient mammals exhibit high proportion of REM sleep and modern mammals show less proportion. The data has been adapted from Jha et al., 2006; Franken et al., 1991; Furano et al., 1995; Siegel et al., 1999; van Twyver and Allison, 1970; Zepelin et al., 2005.

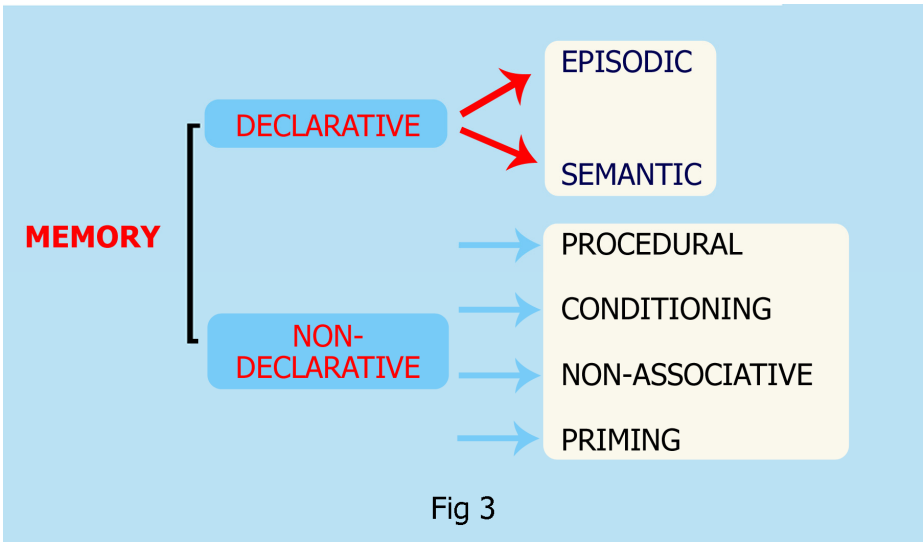

Figure 3. Schematic representation of various types of memories in humans.